REMARKS

Applicant's agent, Elizabeth Hayes-Quebec, telephoned Examiner Blanco on January 17, 2008 to briefly discuss the Response. In the interest of advancing this case to allowance, the Examiner is requested to contact Ms. Hayes-Quebec for a telephone interview in the event he believes that the amended claims are not in condition for allowance.

There are now 20 claims pending.

Claim 1 has been amended to better distinguish the invention over the prior art as discussed below.

Dependent **claims 2, 3, 4, 8, 9, 15, 30, 31, 33 and 35** have been amended for consistency with the limitations recited in claim 1, as presently amended.

Claims 10 and 32 have been converted from dependent claims to independent claims.

Dependent **claim 11** has been amended for consistency with the limitations recited in claim 10, as presently amended.

Claims 29 and 34 have been cancelled without prejudice or disclaimer.

The amendments to the claims are supported in the specification as originally filed. In particular, support for the amendment to claims 30 and 32 may be found explicitly throughout the description, for example, at:

Page 13, lines 21 to 22	The physical properties of the membrane may be modified for example as a function of rehydration, or via the presence of lipids and/or proteins.
Page 14, lines 3 to 10	The membrane of the invention may further comprise/have associated with it various compounds e.g. drugs, biological materials (e.g. peptides/proteins, lipids, etc.), crosslinkers, plasticizers, cytokines, etc. to fulfill or further contribute to an aspect of the desired functionality of the corneal implant in any particular situation. Such agents or compounds may be introduced during the making of the membranes <u>or after their formation.</u> [Emphasis added.]
Page 19, Example 5	A variety of agents or compounds (e.g., crosslinking, plasticizer, drugs, cytokines) can be introduced during the making of the membranes from examples I to IV. Compounds can be introduced either during the mixing of both collagen and pNIPAAm <u>or after the formation of a membrane. The latter can be dried, thereby, the agents can be introduced during the rehydration process.</u> Otherwise, the agents can be introduced on the rehydrated membrane. [Emphasis added.]
Page 20, lines 11 to 13	Albumax (a lipid rich bovine serum albumin, ...) <u>can be added during rehydration</u> with Hank's balanced salt solution (HBSS). [Emphasis added.]
Table I	Albumax (2x)

No new subject matter has been added.

<u>35 USC §102(b)</u>

Claims 1 to 4, 8 to 10 and 29 to 33 have been rejected as being allegedly anticipated in view of Takezawa *et al.* (EP 0 387 975). The Examiner maintains that this reference discloses <u>all</u> the features of the instant invention, as claimed. In particular, the Examiner states that although Takezawa *et al.* disclose a "cell growth substrate", patentable distinction cannot be given to the recitation "corneal implant" in the preamble of the claims (*Kropa v. Robei*, 88 USPQ 478).

The Examiner further states that even though the invention has been defined by a process, determination of patentability is based on the product itself. Therefore, if the product in the product-by-process claim is the same or obvious to a product in the prior art, then the claim is unpatentable even though the product was made by a different process (*In re Thorpe*, 227 USPQ 964).

Claims 1, 4, 10, 15, 25, 26 and 30 to 33 have also been rejected as being allegedly anticipated in view of Chudzik *et al.* (US 6,410,044). Chudzik *et al.* discloses a crosslinkable macromer system comprising a polymer backbone to which are covalently bonded both pendant polymerizable groups and initiator groups. The crosslinkable macromer system is for use as a crosslink matrix between a tissue site (*i.e.* host tissue) and an implant or prosthetic device, *i.e.* as an interface or "grout", to permit tissue growth through the crosslink matrix and between the tissue site and implant. The Examiner contends that claim 1 recites "comprising" which is an open-ended term and therefore includes additional unrecited elements or method steps as disclosed in this reference.

Claims 1, 2, 4, 8, 10, 25, 26 and 30 to 33 have also been rejected as being allegedly anticipated in view of Manesis (US 5,401,508). Manesis discloses a hydrogel composition for use as a corneal implant comprising water, a copolymer (*e.g.* an alkyl acrylamide and an alkyl acrylate ester) and a cross-linking agent. The hydrogel is cured by subjecting it to gamma radiation. Fibronectin is covalently bonded to the polymeric material of the corneal onlay. The Examiner alleges that the process steps by which the corneal implant is defined in claim 1 cannot be considered as claim limitations to distinguish the product over this prior art reference.

Claim 1 has been amended as follows:

> A corneal implant for improving or correcting vision comprising a membrane[[,]] saturated with a hydrating solution, said membrane ~~formed from a solution of~~ consisting essentially of a dried solution of a mixture of a biological polymer ~~mixed with~~ and a polyacrylamide homopolymer[[,]] ~~wherein said solution has been dried to form a membrane and the membrane has been hydrated for use as a corneal implant~~.

Claim 10 has been amended as follows:

> ~~The implant of claim 1, wherein said membrane further comprises~~ A corneal implant for improving or correcting vision comprising a membrane saturated with a hydrating solution, said membrane consisting essentially of a dried solution of a mixture of a biological polymer, a polyacrylamide homopolymer, and a chemical crosslinking agent ~~a chemical crosslink~~.

Claim 30 has been amended as follows:

> The implant of claim 1, wherein the ~~membrane is hydrated with a~~ hydrating solution ~~comprising~~ comprises a drug, a bioactive compound, a chemical crosslinking agent or a combination thereof.

Claim 32 has been amended as follows:

> ~~The implant of claim 1, wherein the mixture of the biological polymer and the polyacrylamide further comprises~~ A corneal implant for improving or correcting vision comprising a membrane saturated with a hydrating solution, said membrane consisting essentially of a dried solution of a mixture of a biological polymer, a polyacrylamide homopolymer, and a drug, a bioactive compound, or a combination of (i) a drug and a bioactive compound, (ii) a drug and a chemical crosslinking agent, (iii) a bioactive compound and a chemical cross-linking agent, or (iv) a drug, a bioactive compound and a chemical crosslinking agent ~~thereof~~.

Claims 2 to 4, 8, 9, 15, 25, 26, 30, 31 and 33 are amended by virtue of their dependency, either directly or indirectly, to claim 1, as presently amended.

Claim 29 has been canceled thus rendering the rejection thereto moot.

The "hydrating solution" recited in the amended claims is supported throughout the specification, for example, at page 13, lines 21 to 22; page 16, lines 22 to 27; page 17, lines 29 to 31; page 18, lines 1 to 4; and page 19, lines 4 to 12 (i.e. Example 5).

Applicant respectfully submits that claims 1, 10, 32 and dependent claims therefrom, are novel and patentably distinguishable over the prior art in view of the following comments.MPEP §2131 provides that:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The **identical invention** must be shown in as complete detail as contained in the ... claim." [Emphasis added.] *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim.

MPEP §2121.01 also provides that:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an **'enabling disclosure'** (...) ." *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). [Emphasis added.].

Applicant respectfully submits that the claimed invention is novel and patentably distinguishable over Takazawa *et al.*, Chudzik *et al.* and Manesis.

In contrast to the prior art, the claimed invention is directed to a **corneal implant** comprising a membrane **saturated with a hydrating solution**, the membrane consisting essentially of a dried solution of a **mixture** of a biological polymer and a polyacrylamide **homopolymer**. Drying of the mixed polymer solution produces an interpenetrating hydrogel network which strengthens and stabilizes the formed membrane **without any chemical bonds**. **Saturation** of the dried membrane with a hydrating solution alters its physical properties centrally required for functionality (*e.g.* optical clarity), pliability (*e.g.* easy for the surgeon to manipulate/handle) and wearability (*e.g.* wettable) as a corneal implant.

For the sake of emphasizing the novelty and patentable distinction of the invention over the prior art, the following table provides a side-by-side comparison of the key features of the claimed invention to the products disclosed in Chudzik *et al.* and Manesis:

Element	Invention	Chudzik *et al.*	Manesis
Product	Corneal implant	Macromer system used as a "grout" between an implant/device and adjacent tissue	Hydrogel compositions comprising water and at least one copolymer
Corneal Implant	Yes	No	Yes
Polymer type	**Homopolymer**	Copolymer	Copolymer
Polyacrylamide Homopolymer	Yes	No	No
Polymer Composition	Polyacrylamide homopolymer and biological polymer <u>**mixed**</u> together	Pendent initiator groups and pendent polymerizable groups (*e.g.* acrylamide) covalently bonded to a polymer backbone (*e.g.* collagen)	N,N-dimethylacryl-amide, N,N-diethylacrylamide, N-methyl, N-ethyl-acrylamide and mixtures thereof; alkylacrylates, alkylmethacrylates and mixtures thereof; and a cross-linking agent
Polymerization	<u>**Drying**</u> of polymer mixture	Free radical; polymeric pendant initiator - attached to same/different polymer backbone	Free radical initiated by ultraviolet or high-energy radiation
Glycoproteins	Collagen	Collagen	Collagen
Glycoprotein Application	<u>**Mixed**</u> in aqueous polymer composition	Polymer backbone of the macromer system to which polymerizable and initiator groups are covalently bonded	Covalent bonding of the cytophilic component onto the corneal onlay
Cross-linking agent	Carbodiimide (EDC) or N-hydroxysuccin-imide (NHS)	Pendent polymerizable groups	Acrylic and/or methacrylic derived multiesters
Cross-linking application	**Chemical**	Light-activated free-radical polymerization initiator	Gamma radiation

Referring firstly to **Chudzik *et al.***, this references clearly does not anticipate the claimed invention. The macromer system disclosed in this reference is a **copolymer** comprising a polymer backbone (*e.g.* collagen) to which pendent polymerizable groups and pendent initiator groups are **covalently bonded**. The macromer system is for **use as a crosslink matrix (*e.g.* grout)** between a tissue site (*i.e.* host tissue) and an implant or prosthetic device.

Manesis also clearly does not anticipate the claimed invention. The hydrogel composition disclosed in this reference is for **use as a corneal onlay** and comprises water and a **copolymer**. The biological polymer (*e.g.* fibronectin) is **covalently bonded** to the copolymeric material of the corneal onlay.

Referring now to **Takezawa *et al.***, this reference describes a cell culture substrate comprising, among other things, collagen and pNIPAAm to support human dermal fibroblast cells. The purpose of their research was to make a polymer substrate of spheroids in cell culture so that the polymer property can be changed as a function of temperature (LCST). The reference discloses that the cell substrate for cell growth/proliferation and detachment avoids problems associated with prior cultured cell recovery processes such as deterioration of cellular functioning, complication of operation, and risk of contamination. These prior processes make use of cell detaching agents such as trypsin, collagenase and EDTA which not only cause significant damage to the cell function, but also are a crucial obstacle to the cell culture process. The problem was solved using a polymer substrate of spheroids in cell culture so that the polymer property can be changed as a function of temperature (LCST). The advantage is that the cell sheet and/or clusters grown on the polymer substrate can be removed by **merely changing the temperature** of the substrate (*i.e.* lowering the temperature below the LCST). This conformational or physical change in the polymer molecules permits the cells to be detached without the use of proteolytic enzymes such as trypsin which is known to destroy bonds between neighbouring cells and compromise cell function.

For the sake of emphasizing the novelty and patentable distinction of the invention over the prior art, the following table provides a condensed summary of the key features of the claimed invention compared to the Takezawa *et al.* polymer substrate produced in Examples 1 to 19:

Examples / **Elements**	**1**	**2**	**3**	**4**	**5**	**6, 18**	**7, 12, 19**	**8, 10, 13 to 16**	**9**	**11**	**17**
Corneal Implant for Improving or Correcting Vision	X	X	X	X	X	X	X	X	X	X	X
Polyacrylamide Homopolymer	✓	✓	✓	X	✓	X	✓	✓	✓	X	✓
Copolymer	X	✓	✓	✓	X	✓	X	X	X	X	X
Biological Polymer	X	X	X	X	X	X	✓	✓	✓	✓	X
Dermal Fibroblast Suspension - Added to Polymer Mixture	X	X	✓	✓	X	X	X	X	X	X	X
Dried Solution of Polymer Mixture	X	X	X	X	✓	✓	✓	✓	✓	✓	X
Dermal Fibroblast Suspension - Poured onto Coated Culture Dish	X	X	X	X	✓	✓	✓	✓	X	✓	X
Dried Polymer Mixture Saturated with Hydrating Solution	X	X	X	X	X	X	X	X	X	X	X

The elements in **bold** are recited in claim 1 of the instant application.

As can be concluded from the above table, no where in the Takezawa *et al.* reference is there disclosed a single example of a corneal implant for improving or correcting vision comprising a membrane saturated with a hydrating solution, said membrane consisting essentially of a dried solution of a mixture of a biological polymer and a polyacrylamide homopolymer.

Again, Applicant points out that a discussion of the nature and purpose of the "hydrating solution" may be found throughout the specification, for example, at page 13, lines 21 to 22; page 16, lines 22 to 27; page 17, lines 29 to 31; page 18, lines 1 to 4; and page 19, lines 4 to 12 (i.e. Example 5).

Further, not only does Takezawa *et al.* **not** teach or even remotely suggest saturating their dried cell substrate with a "hydrating solution", but a skilled person would not even reasonably infer this information from reading the reference in its entirety. More specifically, problems previously encountered with prior cell detachment processes are avoided by using the Takezawa *et al.* polymer substrate because cell detachment can be achieved **without** the addition of **solutions** and/or agents. Because the Takezawa *et al.* cell detachment process is controlled by merely lowering the temperature of the cell culture to below the LCST of the polymer substrate, the risk of contamination from employing solutions required in a cell washing step are avoided altogether (*see*, page 7, lines 26 to 29):

> Furthermore, this invention can significantly simplify the prior complex cell detaching process where the cell washing process and trypsin adding process are necessary. This means that this invention can markedly reduce the **possibility of contamination which is a lethal problem in cell culture technology**. [Emphasis added.]

Accordingly, Takezawa *et al.* does **not** disclose a membrane saturated with a "hydrating solution".

In view of the above comments, Applicant asserts that claims 1, 10, 32 and all dependent claims therefrom, are clearly novel and patentable distinguishable over Takazawa *et al.*, Chudzik *et al.* and Manesis.

Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

35 USC §103(a)

The Examiner has reapplied Chudzik *et al.* against claims 15, 29, 34 and 35 separately, and in combination with Perez *et al.* (*i.e.* claims 5, 13 and 14), Graham *et al.* (*i.e.* claims 11 and 12) and Takezawa *et al.* (*i.e.* claims 2 and 3) for obviousness. Applicant disagrees that the claims, as presently amended, are obvious in view of the prior art references.

As discussed *supra* (see (102(b) rejection), claim 1 has been amended to specify that the **corneal implant** comprises a membrane **saturated with a hydrating solution,** the membrane consisting essentially of a dried solution of a **mixture** of a biological polymer and a polyacrylamide **homopolymer**.

Dependent claims 2, 3, 5, 12 to 15 and 35 have similarly been amended by virtue of their dependency, either directly or indirectly to claim 1, as presently amended. Dependent claim 11 has been amended by virtue of its dependency to claim 10, as presently amended.

Claims 29 and 34 have been cancelled thus rendering the rejections thereto moot.

The Chudzik *et al.* reference is discussed *supra* (see 102(b) rejection).

For the sake of emphasizing that the invention is non-obviousness and patentably distinct over the prior art, the following table provides a side-by-side comparison of the key features of the claimed invention to the products disclosed in Chudzik *et al.*, Perez *et al.* and Graham *et al.*:

Element	Invention	Chudzik *et al.*	Perez *et al.*	Graham *et al.*
Product	Corneal implant	Macromer system used as a "grout" between an implant/device and adjacent tissue	Corneal implant	Corneal implant
Implant Type	Corneal implant	Tissue integration	Corneal Implant	Corneal implant
Product Features	**Mixture** of polyacrylamide homopolymer and biological polymer	Optimal combination of macromer properties controllable by polymerizable groups and polymer backbone	2-layer composite: Corneal tissue or collagen and a hydrogel (crosslinked or glued together)	2-layer composite: Hydrogel composition containing water, covalently bonded to a coating of a synthetic polymeric material
Polymerized Composition	No	Yes	Yes	Yes
Polymer type	Homopolymer	Copolymer	Homopolymer or copolymer	Homopolymer or copolymer
Polyacrylamide Homopolymer	Yes	No	Suggested, but not taught	Suggested, but not taught
Polymer Composition	**Polyacrylamide homopolymer** and **biological polymer** mixed together	Pendent initiator groups and pendent polymerizable groups (*e.g.* acrylamide) covalently bonded to a polymer backbone (*e.g.* collagen)	Crosslinked polymer, *e.g.* polyethylene oxide (PEO), hydroxyethyl-methacrylate (HEMA), polyacrylamide	A lens body comprising a hydrogel composition and water bonded to a coating of a synthetic polymer and cytophilic component
Glycoproteins	Collagen	Collagen	Collagen	Collagen
Glycoprotein Application	**Mixed** in polymer solution	Polymer backbone of macromer system to which polymerizable and initiator groups are <u>covalently bonded</u>	Synthetic hydrogel is <u>covalently attached</u> to a thin collagen matrix.	<u>Covalent bonding</u> of derivatized cytophilic component to the core of the implant
Polymerization	**Drying** of polymer solution	Free radical; polymeric pendent initiator - attached to same/different polymer backbone	Free radical initiator and polymerizing acrylamide or bis acrylamide	Plasma grafting, gamma radiation
Cross-linking agent	Carbodiimide (EDC) or N-hydroxysuccin-imide (NHS)	Pendent polymerizable group	Electron-beam crosslinkable polymer, *e.g.* synthetic PEO	Difunctional component, *e.g.* glutaraldehyde, EDC or polymerizable component
Cross-linking application	**Chemical**	Light-activated free-radical polymerization initiator	Electron-irradiation induced crosslinking	Plasma grafting

As can be seen above, **Perez *et al.*** describe a **two-layer** composite material composed of a hydrogel and a thin layer of corneal tissue or collagen matrix. The hydrogel is formed from an electron-beam crosslinkable polymer that is directly **covalently attached** to the collagen matrix (*i.e.* glycoprotein), or an intermediate material is used to adhere the hydrogel and the collagen matrix together.

Graham *et al.* also describe a **two-layer** corneal implant comprising a lens body and a porous core having an outer surface made of a hydrogel composition containing water and a hydrophilic polymeric material. A **coating of a synthetic polymeric material** is located on the outer surface of the core and **covalently bonded** to the hydrogel composition. Furthermore, the glycoprotein (*i.e.* cytophilic component) is **covalently bonded** to the implant.

In order to establish a prima facie case of obviousness, the prior art references(s) must teach or suggest all of the elements and limitations recited in the claims.

As a first issue, one of skill in the art would not read the Takezawa *et al.* reference since it relates to a non-analogous field of scientific endeavour and therefore, can not be used individually, or in combination with any other reference, to establish a *prima facie* case of obviousness. A person interested in fabricating an artificial corneal implant for improving or correcting vision would **not** look for guidance in the field of cell culture substrates.

Secondly, as is clearly evident from the tabled information above, Applicant respectfully submits that neither Chudzik *et al.* separately, or in combination with Perez *et al.* and Graham *et al.* teach or suggest **all** of the elements and limitations recited in the claimed invention.

There is no suggestion, teaching or motivation to combine the references.

Applicant further submits that a person of skill in the art would not have been motivated to arrive at the invention, as claimed in view of Chudzik *et al.* separately, or in combination with Perez *et al.*, Graham *et al.* and Takezawa *et al.*

It is well established under U.S. patent law that in order to establish a *prima facie* case of obviousness, there must be a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. There must be evidence that "a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed". ("[A] rejection cannot be predicated on the mere identification ... of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.") (*In re Werner Kotzab,* 217 F.3d 1365, 1371 (Fed.Cir.2000)).

The Examiner's only argument is to point out that the features of the invention are either disclosed in these references or are "known in the art" without particularizing where exactly the teaching, suggestion or motivation is disclosed in these references to support the rejection. In other words, the Examiner has not explained or articulated explicit or factual findings as to how the prior art would have suggested to a skilled person to make changes to any of the references necessary to arrive at Applicant's invention that would support a 35 U.S.C. §103 rejection.

The prior art teaches away from combining references.

A finding that a prior art reference "teaches away" from combining references can alone defeat an obviousness claim. *Winner Int'l Royalty Corp. v. Wang,* 202 F.3d 1340, 1349-50 (Fed.Cir.2000) (citing *Gambro Lundia AB v. Baxter Healthcare Corp.,* 110 F.3d 1573, 1579 (Fed.Cir.1997)). "A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH,* 139 F.3d 877, 885 (Fed.Cir.1998) (quotation omitted).

For example, in Chudzik *et al.*, this reference indicates that the macromer systems employ polymeric initiators because they provide a number of unexpected advantages over the use of polymerizable macromers (*see*, col. 6, lines 31 to 42):

> Macromer systems of the present invention, employing polymeric initiators, provide a number of unexpected advantages over the use of polymerizable macromers and separate, low molecular weight initiators. Such systems, for instance, provide an optimal combination of such properties as nontoxicity, efficiency, and solubility. Solubility, for instance, can be improved by virtue of the ability to control the aqueous or organic solubility of the polymerizable macromer by controlling the backbone. Toxicity can also be improved, since the polymeric initiators of this invention typically cannot diffuse into cells in the course of immobilization.

Accordingly, Chudzik *et al.* clearly teaches away from producing a corneal implant comprising a membrane made **only** by mixing polyacrylamide homopolymer (*i.e.* an **inert**, established polymer) and a biological polymer, *i.e.* without the use of polymeric initiators.

Referring to **Perez et al.**, this reference focuses on the issue of biological activity, *i.e.* cell and tissue response, of synthetic surfaces in corneal surgery and that the growth of the epithelium over the implant is important (*see*, page 3, lines 16 to 25):

> Upon the re-evaluation of the concept of a prosthetic cornea, the issue of biological activity, *i.e.*, cell and tissue response, of synthetic surfaces became a consideration. In either therapeutic or refractive corneal surgery, the growth of epithelium over the implant is important. Normally, the epithelium is a labile cellular population which will grow back over a denuded area of the cornea. Thus, a synthetic corneal surface must provide an environment that is conducive to epithelial cell growth.

They note that collagen coating of conventional hard poly(methylmethacrylate) corneal prostheses increases the attachment of these devices to tissue and decreases the inflammatory responses. Therefore, they deduce that a hydrogel material must be constructed possessing a surface environment conducive to corneal epithelial cell growth in addition to maintaining other desirable characteristics of hydrogels (*see*, page 7, line 35 to page 8, line 2):

> Ideally, a hydrogel material must be constructed possessing a surface environment conducive to corneal epithelial cell growth in addition to maintaining other desirable characteristics of hydrogels. This has not yet been achieved.

Perez *et al.* further disclose (*see*, page 8, lines 16 to 24):

> A two-layer composite material composed of a thinlayer of corneal tissue or collagen and a hydrogel, preferably formed of an electròn-beam crosslinkable polymer such as a synthetic polyethylene oxide (PEO) hydrogel, is described. The material is designed to provide a suitable substrate for corneal epithelial cell growth while mainlining the desirable characteristics of hydrogels, i.e., clarity, flexibility and ability to allow diffusive flow of nutrients.

Perez *et al.* also emphasize (*see*, page 9, line 32 to page 10, line 5):

> The design rationale is to construct a material possessing a surface environment conducive to epithelial cell growth in addition to possessing the proper optical, diffusive, and mechanical characteristics of the cornea. In the preferred embodiment, electron-irradiation-induced (EII) crosslinking is used to synthesize a hydrogel network and simultaneously attach the polymeric network to a collagenous substrate.

The role of the collagen substrate is repeatedly described throughout the reference (*see*, for example, page 11, line 35 to page 12, line 1):

> ... electron-irradiation induced (EII) crosslinking is used to crosslink a hydrogel network onto a collagenous matrix substrate, which serves as a substrate for cell growth.

Thin layers of corneal tissue are grafted on the surface of the hydrogel to form a suitable surface for cell growth and to impart added mechanical stability to the implant (*see*, for example, page 12, line 23 to page 13, line 7). This approach allows conservation of the tissue architecture (*see*, page 14, line 8 to page 15, line 3).

It is further described that the advantage to using electron-radiation induced crosslinking is that it does not require the solubilization of the tissue and therefore, the native architecture is preserved in the final device (*see*, page 15, lines 4 to 8).

Accordingly, Perez *et al.* clearly teaches away from producing a corneal implant comprising a membrane made **only** by mixing polyacrylamide homopolymer and a biological polymer, *i.e.* a composition of a polyacrylamide mixed with collagen that can be crosslinked with a chemical crosslinking agent; not grafted layers of collagen to the surface of a hydrogel crosslinked by EII.

Referring to **Graham *et al.***, the importance of the synthetic coating is described in this reference:

> The cell migration value is one important measure of the cell growth and adhesion on the material. The higher the cell migration value the higher the protein adsorption affinity and the greater the ability of a material to support cell, for example, epithelial cell growth. (*see* Col. 9, lines 24 to 29.)
>
> Placing the cytophilic component directly on the hydrophilic polymeric component results in only relatively minor, if any, cell migration value enhancement. See Lenses 22 to 25. (*see* Col. 11, lines 47 to 50 and Table 3.)

Accordingly, because covalently bonding the cytophilic component, such as collagen, to the core of the corneal implant is important for cell migration, Graham *et al.* clearly teaches away from **mixing** a solution of the cytophilic component (*e.g.* collagen) with a polyacrylamide homopolymer to form a polymer membrane for use as an implant.

Further disclosed in Chudzik *et al.*, Perez *et al.* and Graham *et al.* is the use of light, electron beam free-radical polymerization or gamma/plasma-irradiation to polymerize their polymer compositions. However, the presence of free-radical initiators, when activated, produce free radicals having distinct cytotoxic potential. A skilled person interested in designing a biocompatible corneal implant would not look to using materials and methods that can be detrimental to the activity of biological materials and can complicate production methods. In other words, these references teach away from the polymer composition as claimed which does not employ the use of an initiator, free-radical polymerization or gamma/plasma-irradiation to produce the polymer product. The

bulk material is produced **<u>only</u>** by mixing polyacrylamide homopolymer and a biological polymer, such as collagen.

No reasonable expectation of success.

In view of the foregoing comments, Applicant submits that a skilled person would not have any reasonable expectation of success that the combination of Chudzik *et al.* separately, or in combination with Perez *et al.*, Graham *et al.* and Takezawa *et al.* would work to produce beneficial results or that a person of skill in the art should be able to arrive at a claimed invention through a minimum of experimentation.

Claims 2, 3, 5, 11 to 15 and 35 are Inventive Over The Prior Art

Accordingly, Applicant submits that the instant invention, as presently claimed, is inventive and patentably distinguishable over the prior art and that the Examiner has not established a *prima facie* case of obviousness based on the cited prior art references.

Reconsideration and withdrawal of the rejections are respectfully requested.

In view of the foregoing, early favourable consideration of this application is earnestly solicited. It is believed this responds to all of the Examiner's concerns. However if the Examiner believes that the claims do not overcome any of the rejections and/or does not consider that the application is in a form for allowance, then he is requested to contact, Elizabeth A. Hayes-Quebec (Reg. No. 48,305) at 613-232-2486 to discuss the matter.

Respectfully submitted,

CHARLES J. DOILLON, ET AL

By RADowell / 10705

Ralph A. Dowell
Reg. No. 26,868
Tel.: (703) 415-2555
Fax: (703) 415-2559

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EAH:pw

Correspondence address
Dowell & Dowell, P.C.
Suite 406
2111 Eisenhower Ave.
Alexandria, VA 22314
U.S.A.